REMARKS

Applicants respectfully request reconsideration. Claims 1, 5, 8-13, 20-33 and 35 were previously pending in this application. By this amendment, Applicants are canceling claim 5 without prejudice or disclaimer. Claim 1 has been amended. Support for this amendment can be found at least in previously pending claim 5. As a result, claims 1, 8-13, 20-33 and 35 are pending for examination with claim 1 being an independent claim. No new matter has been added.

Summary of Interview with Examiner

Applicants thank Examiner Parkin for conducting a telephone interview with Applicants' representatives Helen Lockhart and Brenda Luciano on January 24, 2006.

During the interview the issues of the rejection under 35 USC 112 was discussed. In particular Applicants agreed to amend claim 1 to introduce the limitation of claim 5 in order to overcome the new matter rejection. Applicants also discussed the response to the previous office action in detail and reviewed the scientific basis for the arguments. The Declaration of Dr. Heather Davis was reviewed point by point. The Examiner indicated that Applicants arguments were reasonable especially in view of the declaration data submitted by Applicants with the previous office action response and that he would discuss the issues with his supervisor.

Rejections under 35 U.S.C. §112

New Matter:

Claims 1, 5, 8-13, 20-33 and 35 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing new matter. The Examiner states that applicants "may obviate the rejection by appropriate amendment of the claim language." Without conceding the Examiner's position and in the interest of furthering prosecution of this case, claim 1 has been amended to recite the limitations previously presented in claim 5 as discussed in the interview. Claim 5 has subsequently been cancelled.

Accordingly, withdrawal of the rejection of claims 1, 5, 8-13, 20-33 and 35 under 35 U.S.C. §112 is respectfully requested.

Written Description:

Claims 1, 8-13, 20-33 and 35 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to meet the written description requirement. The Examiner states that the "issue raised in this application is whether the original application provides adequate support for the broadly claimed genus of modified nondescript CpG dinucleotides, non-saponin adjuvants, and antigen".

As discussed in the interview, the specification provides a description of the claimed invention sufficient to demonstrate to one of skill in the art that Applicants had possession of the invention at the time of filing of the application. The claimed invention is directed to a method of stimulating an immune response using a synergistic combination of immune stimulating adjuvants (now limited to a select group) and CpG oligonucleotides. The specification provides adequate written support for the combination of CpG oligonucleotides and immune stimulating adjuvant. For instance, the class of CpG oligonucleotides useful according to the invention is described in the specification. Each of the immune stimulating adjuvants listed in claim 1 are well described. For example the paragraph beginning on page 19, line 14 of the instant specification describes the class of immune stimulating adjuvants. Numerous working examples also demonstrate synergistic immune responses between CpG oligonucleotides and adjuvants. Example 1 of the instant specification details the synergistic effect of combining CpG and alum. Example 2 describes a similar effect with CpG and MPL. Example 4 describes the synergistic Th1 immune response resulting from a combination of CpG and IFA, an adjuvant which, similarly to alum, typically produces Th2 results when used alone.

Thus, the disclosure provides written description for the method of using a CpG oligonucleotide and a non-nucleic acid immune stimulating adjuvant. Accordingly, withdrawal of the rejection of claims 1, 8-14, 20-33, and 35 under 35 U.S.C. §112 is respectfully requested.

Enablement:

Claims 1, 5, 8-13, 20-33 and 35 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to meet the enablement requirement.

According to the Examiner the "disclosure fails to provide adequate guidance pertaining to the structural requirements of any given 'modified' ISS-ODN" and "pertaining to those immune stimulating adjuvants (e.g., saponins, MPL, MDP, etc.) that can reasonably be expected to produce a synergistic immune response when combined with another adjuvant." According to the Examiner the "prior art is unpredictable and teaches that many putative ISS elements do not function in the manner desired and often fail to facilitate immune responses to the immunogen of interest."

Applicants respectfully disagree with the application of the legal requirements to the claims being presented in the office action as well as the characterization of Applicants' data in the specification and the Declaration of Dr. Davis. Where are these teachings of unpredictability found in the art? The references of record do not establish the unpredictability of a phosphate backbone modification or that many "putative ISS elements do not function in the manner desired."

The Examiner has the initial burden of establishing the reasons for lack of enablement. The examiner must present evidence or explain why the accuracy of Applicants' assertions are doubtful. See MPEP section 2164.04:

> "In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 USC 112 first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the

> truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370."

In the instant case there is absolutely no evidence of record to establish this "known unpredictability." The Examiner has not met his burden in establishing the rejection for lack of enablement. Mere conclusions as to the known unpredictability in the art is not sufficient.

Regardless, Applicants have presented evidence sufficient to rebut a prima facie rejection for lack of enablement. The claimed CpG oligonucleotides all have the common structural property that they include an unmethylated CpG dinucleotide. This class of oligonucleotides is known and has been described extensively in patents and patent applications. It is the unmethylated CpG dinucleotide that confers the immune stimulating properties on the oligonucleotide. It is now believed that CpG oligonucleotides act through a common cellular receptor, TLR9. It is believed that CpG oligonucleotides are recognized by TLR9 and that this leads to the promotion of an immune response in which a Th1 response is favored. It is this common mechanism that unifies the resultant immune response produced by CpG oligonucleotides.

The Examiner has indicated that "various phosphate backbone modifications can have unpredictable effects on the adjuvant activities of any given CpG ODN." The specification provides guidance for the type of phosphate backbone modifications that can be incorporated in the CpG oligonucleotides of the invention. Applicants have provided sufficient reasons for why one of skill in the art would expect the claimed class of CpG oligonucleotides to function in the manner set forth in the claims. The Examiner has not provided any evidence or adequate reasoning why one of skill in the art would doubt this assertion.

Applicants also disagree with the characterization of data in the specification and the Declaration of Dr. Davis. It is asserted in the Office Action (page 7) that the specification "provides a limited working embodiment involving a single antigen/immunogen (e.g. HBSAg) and adjuvant (e.g. alum), and a limited number of CpG ODNs (e.g., #1826, #2006, #1968)." The specification, however, includes several examples testing different CpG ODN and different adjuvants. Example 1 of the instant specification details the synergistic effect of combining CpG

and alum. Example 2 describes a similar effect with CpG and MPL. Example 4 describes the synergistic Th1 immune response resulting from a combination of CpG and IFA, an adjuvant which, similarly to alum, typically produces Th2 results when used alone.

The Examiner has also stated that "while the declaration of Dr. Hunter provided some evidence for a synergistic immune response between a specific combination of CpG ODN, adjuvant, and immunogen (e.g. CpG-1826, alum, and HBSag), it also demonstrated that many combinations of ISS, adjuvant, and immunogen were not synergistic." Applicants disagree. Initially, Applicants point out that the Declaration is by Dr. Heather Davis, an inventor of the claimed invention, not Dr. Hunter. Additionally, the data provided in the declaration demonstrates, as thoroughly described in the instant patent application, that the use of other immune stimulating adjuvants in combination with CpG-ODN results in a synergistic activation of the immune system. Specifically, these data demonstrate synergy between CpG-ODN and immune stimulating adjuvants consistent with the data presented in the Examples of the specification.

The results represented in Exhibit 1 attached to the Declaration of Dr. Heather Davis demonstrated that immune stimulating adjuvants including Montanide ISA 720 (Seppic Inc.), Freund's incomplete adjuvant (FIA), cholera toxin (CT), E. coli heat-labile toxin (LT), cholera toxin subunit B (CTB), the B subunit of Escherichia coli heat labile enterotoxin (LTB), and various detoxified LT (LTK63, LTE112K, LTS61F, LTR192G, or LTA69G), and MF-59 produced synergistic immune responses when combined with representative CpG-ODN including CpG-ODN 1826 (SEQ ID NO:86) and CpG-ODN 7909 (SEQ ID NO:77). The Examiner is respectfully requested to point out the data in the declaration that "demonstrated that many combinations of ISS, adjuvant, and immunogen were not synergistic."

Applicants have provided strong evidence that the breadth of the claims is adequately supported by the disclosure. Applicants have provided guidance in the specification for the use of immune stimulating adjuvants. Immune stimulating adjuvants are described in detail on page 6 lines 2-4, and further on page 19 lines 12-22. Immune stimulating adjuvants are defined as "an adjuvant that causes activation of a cell of the immune system" and several representative examples are listed. Example 2 in the specification (page 53, line 30 – page 54 line 1) illustrates the

synergistic effect of treatment with CpG-ODN and MPL, an immune-stimulating adjuvant. The corresponding data is shown in Figure 7.

The data and descriptions presented in the specification were adequate to demonstrate to one of skill in the art at the time of the filing of the patent application that CpG oligonucleotides would be useful in combination with other adjuvants for synergistically promoting an immune response. One of ordinary skill in the art, based on the teachings in the patent application, would have reasonably expected the claimed invention to work over the full scope of the claims.

Accordingly, withdrawal of the rejection of claims 1, 5, 8-13, 20-33 and 35 under 35 U.S.C. §112 is respectfully requested.

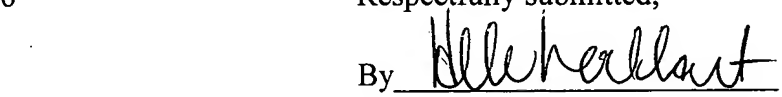
CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: April 6, 2006

Respectfully submitted,

By 

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